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(71) Applicant *(for all designated States except US)*: G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).

(71) Applicant *(for US only)*: ROGERS, Kathy, L. [US/US]; 7431 Arlington Drive, Richmond Heights, MO 63117 (US).

(72) Inventor: ROGERS, Roland, S. (deceased).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TALLEY, John, J. [US/US]; 8772 Pine Avenue, Brentwood, MO 63144 (US).

BERTENSHAW, Stephen, R. [US/US]; 8758 Pine Avenue, Brentwood, MO 63144 (US).

(74) Agents: BULOCK, Joseph, W. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).

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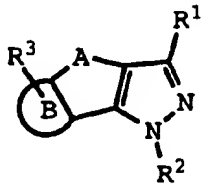
(54) Title: BENZ[g]INDAZOLYL DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of benz[g]indazolyl derivatives is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by Formula (I) wherein A is -CH=CH-; wherein B is phenyl or pyridyl; wherein R^1 is selected from lower haloalkyl, cyano, lower alkoxycarbonyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl and lower N-alkyl-N-phenylaminocarbonyl; wherein R^2 is phenyl optionally substituted at a substitutable position with a radical selected from lower alkylsulfonyl and sulfamyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N,N-dialkylamino and nitro; or a pharmaceutically-acceptable salt thereof.



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BENZ[g]INDAZOLYL DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

The novel compounds described herein are such safe and also effective antiinflammatory agents. The invention compounds are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects. The compounds described herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

Substituted pyrazoles having antiinflammatory activity are described in copending applications 08/160,594 and 08/160,553.

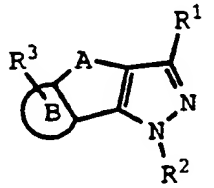
Fused tricyclic pyrazoles having a saturated ring bridging the pyrazole and a phenyl radical have been previously described as HMG-CoA reductase inhibitors in U.S. Patent Nos. 5,134,155 and 5,315,012. Tricyclic pyrazoles have been previously described as antibiotics by M. Hashem et al. [*J. Med. Chem.*, **19**, 229 (1976)].

Tricyclic benz[g]indazoles and 4,5-dihydrobenz[g]indazoles are described as antiinflammatory agents in U.S. Patent No. 3,940,418. R. Hamilton [*J. Heterocyclic Chem.*, **13**, 545 (1976)] describes tricyclic benz[g]indazoles and 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. Specifically, [7-chloro-1-phenyl-1H-benz[g]indazol-3-yl]carboxylic acid and methyl (7-chloro-1-phenyl-1H-benz[g]indazol-3-yl)carboxylate are described.

The invention's unsaturated benz[g]indazolyl derivatives are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects.

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating inflammation-related disorders is defined by Formula I:



(I)

wherein A is $-(CH_2)_m-CH=CH-(CH_2)_n-$;

wherein m is 0 or 1;

wherein n is 0 or 1;

wherein B is selected from aryl and heteroaryl;

wherein R^1 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, alkoxycarbonyl, carboxyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, aminocarbonyl, alkoxy, alkoxyalkyl, aminocarbonylalkyl, N-monoalkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl and heterocyclic;

wherein R^2 is selected from aryl and heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from alkylsulfonyl, aminosulfonyl, halo, alkyl, alkoxy, hydroxyl and haloalkyl; and

wherein R^3 is one or more radicals selected from hydrido, halo, alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, aminocarbonyl, N-monoalkylaminocarbonyl, N-arylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, aminosulfonyl, N-alkylaminosulfonyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino;

provided R^2 is substituted when R^3 is halo;

or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of

pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, cystic fibrosis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds also would be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis, and of acute injury to the eye tissue. The compounds also would be useful for the treatment of certain central nervous system disorders such as alzheimers disease and dementia. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds also would be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, and pigs, and of birds.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

Suitable LTB_4 inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB_4 inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, masoprocol, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM. Such preferred selectivity may indicate an ability to

reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein A is $-(CH_2)_m-CH=CH-(CH_2)_n-$; wherein B is selected from aryl, and five-six membered heteroaryl; wherein m is 0 or 1; wherein n is 0 or 1; wherein R^1 is selected from halo, lower haloalkyl, cyano, nitro, formyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, amidino, cyanoamidino, lower alkoxy, lower alkoxyalkyl, lower aminocarbonylalkyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylcarbonyl, lower alkylcarbonylalkyl, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkylthioalkyl, lower alkylsulfinylalkyl, lower alkylsulfonylalkyl, lower N-alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-phenylaminosulfonyl and five-seven membered heterocyclic; wherein R^2 is selected from phenyl and five-six membered heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from lower alkylsulfonyl, aminosulfonyl, halo, lower alkyl, lower alkoxy, hydroxyl and lower haloalkyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, aminosulfonyl, lower N-alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five-seven membered heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds consists of those compounds of Formula I wherein A is -CH=CH-; wherein B is selected from aryl and six membered heteroaryl; wherein R^1 is selected from halo, lower haloalkyl, cyano, nitro, formyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxy, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylcarbonyl and lower hydroxyalkyl; wherein R^2 is phenyl optionally substituted at a substitutable position with one or more radicals selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

An even more preferred class of compounds consists of those compounds of Formula I wherein A is -CH=CH-; wherein B is phenyl or pyridyl; wherein R^1 is selected from lower haloalkyl, cyano, lower alkoxycarbonyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl and lower N-alkyl-N-phenylaminocarbonyl; wherein R^2 is phenyl optionally substituted at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino,

lower N,N-dialkylamino and nitro; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Fcrmula I wherein A is -CH=CH-; wherein B is phenyl or pyridyl; wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl and N-methyl-N-phenylaminocarbonyl; wherein R^2 is phenyl optionally substituted at a substitutable position with methylsulfonyl or aminosulfonyl; and wherein R^3 is one or more radicals selected from fluoro, chloro, bromo, methylthio, ethylthio, isopropylthio, *tert*-butylthio, isobutylthio, hexylthio, methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, *tert*-butylsulfinyl, isobutylsulfinyl, hexylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, cyano, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, N-methylaminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, trifluoromethoxy, amino, N,N-dimethylamino and nitro; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-[6-chloro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

[1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carbonitrile;

methyl [1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

ethyl [1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

N-methyl [1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxamide;

6-chloro-7-methoxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

[1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carbonitrile;

methyl [1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

ethyl [1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

N-methyl [1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxamide;

[1-(4-methylsulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;

methyl [1-(4-methylsulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;

[1-(4-methylsulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carbonitrile;

3-(difluoromethyl)-7-hydroxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-7-hydroxymethyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-7-trifluoromethoxy-1H-benz[g]indazole;

7-chloro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-7-fluoro-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
7-bromo-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-7-methyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-7-methoxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-6,7-methylenedioxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-7-dimethylamino-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-6-fluoro-7-methoxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6-chloro-3-(difluoromethyl)-7-fluoro-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6-chloro-3-(difluoromethyl)-7-methyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-6-fluoro-7-methyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6,7-dichloro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6,7-difluoro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-7-methylthio-1H-benz[g]indazole;
6-chloro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-7-methylthio-1H-benz[g]indazole;
3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-7-methylsulfinyl-1H-benz[g]indazole;
6-chloro-3-(difluoromethyl)-7-methylsulfinyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
[1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;

methyl [1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;

[1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carbonitrile;

7-hydroxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

7-hydroxymethyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

1-(4-methylsulfonylphenyl)-7-trifluoromethoxy-3-(trifluoromethyl)-1H-benz[g]indazole;

7-chloro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

7-fluoro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

7-bromo-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

7-methyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

7-methoxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6,7-methylenedioxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

7-dimethylamino-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-fluoro-7-methoxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-7-fluoro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-7-methyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-fluoro-7-methyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6,7-dichloro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6,7-difluoro-1-(4-methylsulfonylphenyl)-3-(trifluorom thyl)-1H-benz[g]indazole;

1-(4-methylsulfonylphenyl)-7-methylthio-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-1-(4-methylsulfonylphenyl)-7-methylthio-3-(trifluoromethyl)-1H-benz[g]indazole;

7-methylsulfinyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-7-methylsulfinyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-7-methoxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

[1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;

methyl [1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;

[1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carbonitrile;

4-[3-(difluoromethyl)-7-hydroxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-hydroxymethyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-trifluoromethoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-chloro-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-fluoro-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-bromo-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-6,7-methylenedioxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-dimethylamino-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-6-fluoro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-fluoro-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-6-fluoro-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6,7-dichloro-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6,7-difluoro-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-methylthio-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-methylthio-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-methylsulfinyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-methylsulfinyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

[1-(4-aminosulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;

methyl [1-(4-aminosulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;

4-[1-(methylsulfonyl)-3-(trifluoromethyl)-1H-pyrazolo[4,3-f]quinoline;

4-[3-(trifluoromethyl)-1H-pyrazolo[3,4-e]isoquinolin-1-yl]benzenesulfonamide;

[1-(4-aminosulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carbonitrile;

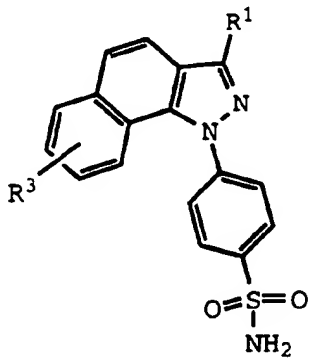
4-[7-hydroxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-hydroxymethyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-trifluoromethoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-chloro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-fluoro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-bromo-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1 yl]benzenesulfonamide;
4-[6,7-methylenedioxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-dimethylamino-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-fluoro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-chloro-7-fluoro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-chloro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-fluoro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6,7-dichloro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6,7-difluoro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-methylthio-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-chloro-7-methylthio-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[7-methylsulfinyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-chloro-7-methylsulfinyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide; and
4-[6-chloro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



(II)

wherein R^1 is hydrido or haloalkyl; and wherein R^3 is one or more radicals selected from alkyl, alkoxy and halo; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R^1 is hydrido or lower haloalkyl; and wherein R^3 is one or more radicals selected from lower alkyl, lower alkoxy and halo; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein R^1 is selected from hydrido, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; and wherein R^3 is one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy and *tert*-butoxy; or a pharmaceutically-acceptable salt thereof.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either

alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each

having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or haloalkoxyalkyl radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Preferred heterocyclic radicals contain 3 to 10 members. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms

[e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] and isothiazolyl; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the

like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like. Said "heterocyclic" radicals may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. More preferred heteroaryl radicals include five to six membered heteroaryl radicals. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl. The term "arylthio" embraces radicals containing an aryl radical, attached to a divalent sulfur atom, such as a phenylthio radical. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "alkylsulfinylalkyl" embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl and alkylsulfinyl are defined as above. More preferred alkylsulfinylalkyl radicals are "lower alkylsulfinylalkyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinylalkyl radicals include methylsulfinylmethyl. The term

"sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "alkylsulfonylalkyl" embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl and alkylsulfonyl are defined as above. More preferred alkylsulfonylalkyl radicals are "lower alkylsulfonylalkyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonylalkyl radicals include methylsulfonylmethyl, ethylsulfonylmethyl and propylsulfonylmethyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl", denote a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The terms "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" denote aminosulfonyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote aminosulfonyl radicals substituted with one aryl radical or one alkyl and one aryl radical, respectively. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include formyl, alkanoyl and aroyl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carbonyl",

whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkylcarbonyl" includes radicals having alkyl radicals attached to a carbonyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. The term "alkylcarbonylalkyl" denotes radicals having alkylcarbonyl attached to alkyl radicals as defined above. More preferred alkylcarbonylalkyl radicals are "lower alkylcarbonylalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such radicals include methylcarbonylmethyl and ethylcarbonylmethyl. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl. The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. More preferred carboxyalkyl radicals are "lower carboxyalkyl" having alkyl portions of one to six carbons. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl,

aminoethyl and aminobutyl. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. More preferred alkylamino radicals are "lower alkylamino" radicals having alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "lower alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "alkylaminocarbonyl" embraces alkylamino radicals, as described above, to a carbonyl radical. More preferred alkylaminocarbonyl radicals are "lower alkylaminocarbonyl" having lower alkylamino radicals, as described above, attached to a carbonyl radical. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl. The terms "N-monoarylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "aminocarbonylalkyl" denotes an aminocarbonyl radical attached to an alkyl radical, as defined above. The term "amidino" denotes an $-C(=NH)-NH_2$ radical. The term "cyanoamidino" denotes an $-C(=N-CN)-NH_2$ radical. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "acylamino" embraces an amino

radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino ($CH_3C(=O)-NH-$).

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formula I.

Compounds of Formula I would also be capable of inhibiting cytokines, such as TNF, IL-1, IL-6, and IL-8. As such, the compounds can be used in the manufacture of a medicament or in a method for the treatment for the prophylactic or therapeutic treatment of diseases mediated by cytokines, such as TNF, IL-1, IL-6, and IL-8.

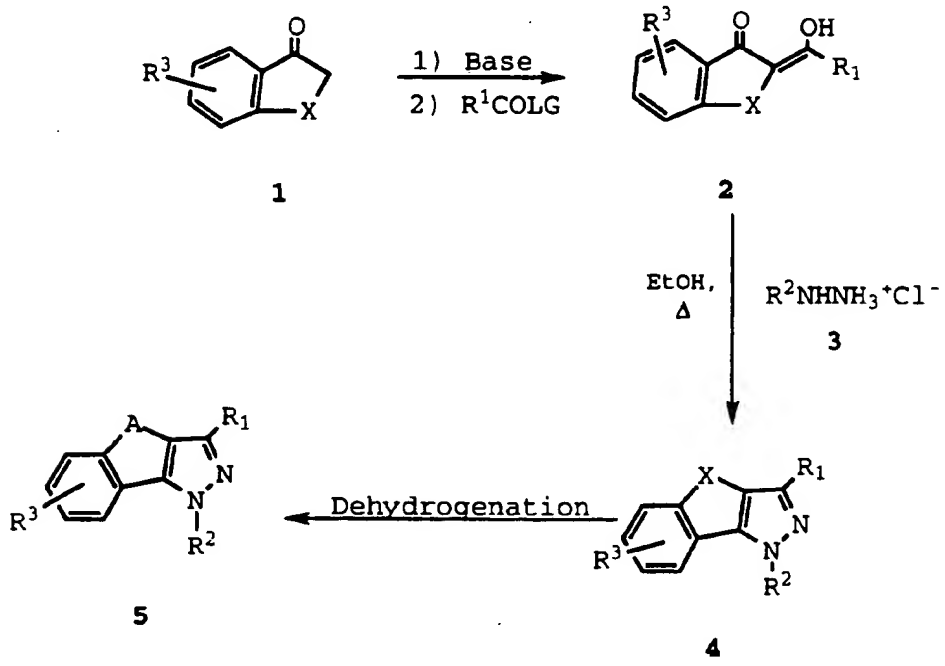
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic,

fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-VI, wherein the R^1-R^3 substituents are as defined for Formula I-II, above, except where further noted.

Scheme I

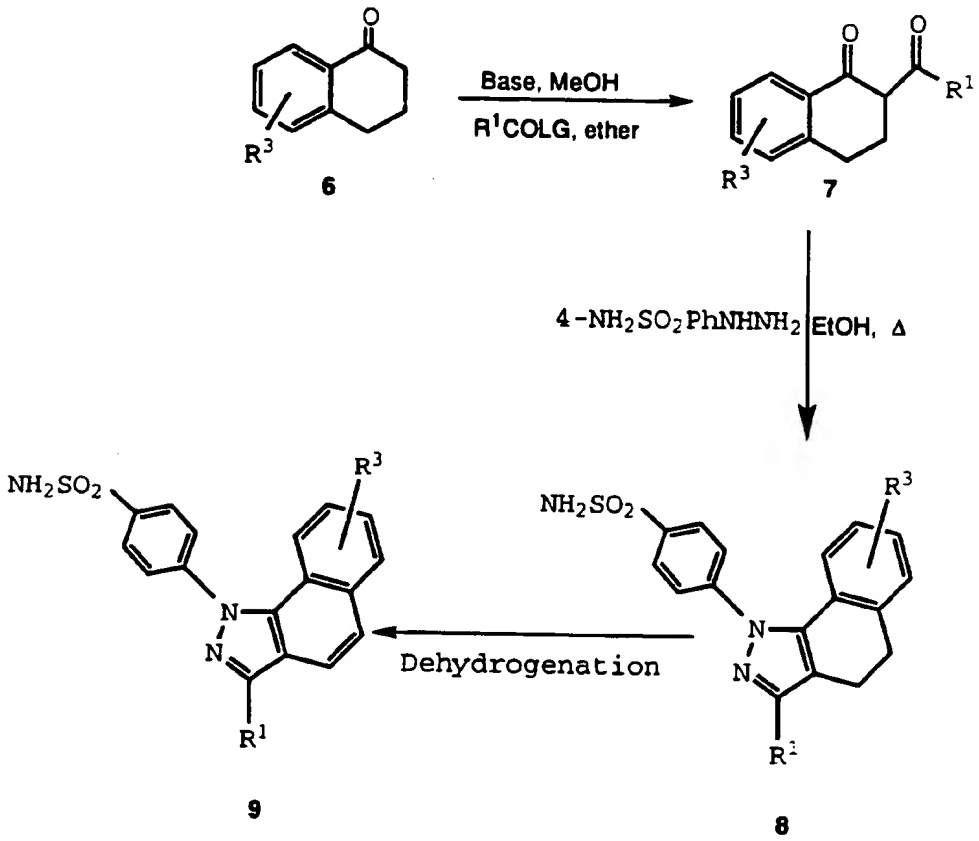


1 2 3 4 5

Synthetic Scheme I shows the three step procedure for preparation of fused pyrazole compounds embraced by Formula I. In step 1, a ketone **1** (where X is $(CH_2)_{2-4}$) is reacted with base, such as a lithium base, for example lithium diisopropyl amide (LDA) or LiHMDS, or sodium methoxide (25%) in a protic solvent, such as methanol, followed by condensation with suitable acylating agents R^1COLG (where LG represents an appropriate leaving group such as methoxy, ethoxy, chloro, imidazole, tosyl and the like), such as ethyl trifluoroacetate, in an appropriate solvent such as diethyl ether, methanol or tetrahydrofuran, to give the intermediate diketone **2** (in the enol form). In

step 2, the diketone **2** in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the free base or hydrochloride salt of a phenylhydrazine **3** at reflux for about 24 hours to afford the fused pyrazole **4**. In step 3, the fused pyrazole **4** is treated with a dehydrogenating agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Additional agent can be periodically added to give the partially unsaturated antiinflammatory compounds **5** of this invention. Dehydrogenation simultaneous with halogenation can be achieved by reacting the dihydro fused pyrazole **4** with N-chlorosuccinimide (NCS) and heating to about 50°C for several days.

Scheme II



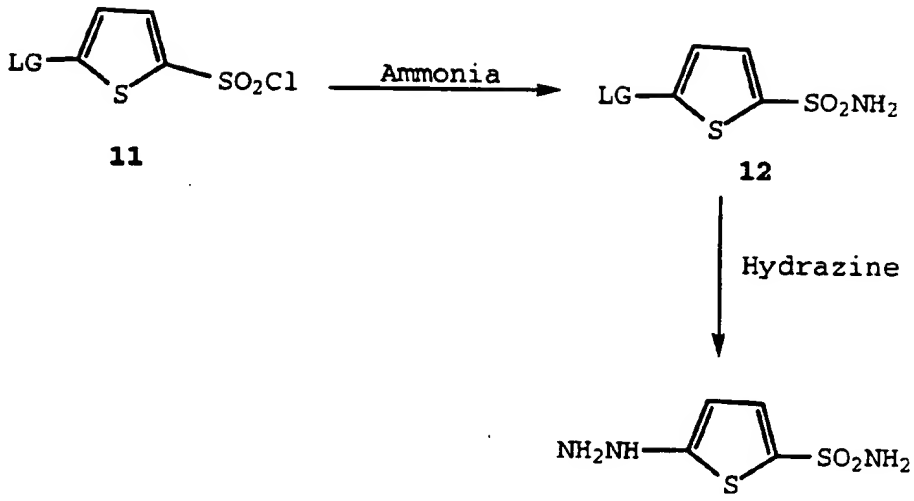
Synthetic Scheme II shows the three step procedure for preparation of benz[g]indazole compounds **9** embraced by Formula I. In step 1, 1-tetralone derivatives **6** are reacted with base, such as lithium diisopropyl amide (LDA) or sodium methoxide (25%) in a protic solvent, such as methanol, followed by condensation with suitable acylating agents R^1COLG (where LG is defined for Scheme I) such as ethyl trifluoroacetate in an appropriate solvent such as diethyl ether, methanol or tetrahydrofuran to give the intermediate diketones **7**. In step 2, the diketones **7** in an anhydrous protic solvent, such as absolute ethanol or acetic acid, are treated with the free base or hydrochloride salt of a phenylhydrazine at reflux for 24 hours to afford the 4,5-dihydro-benz[g]indazoles **8**. In step 3, the 4,5-dihydro-benz[g]indazoles **8** are reacted with DDQ or N-chlorosuccinimide (NCS) and heated to an appropriate temperature. Additional reagent can be periodically added to give the antiinflammatory compounds **9** of this invention.

SCHEME III

10 **3**

Synthetic Scheme III illustrates a procedure used to prepare the substituted phenylhydrazine hydrochlorides **3** as used in Schemes I-II. The substituted phenylhydrazine is converted to the hydrochloride salt by stirring with a 4N solution of hydrochloric acid in a solvent such as dioxane.

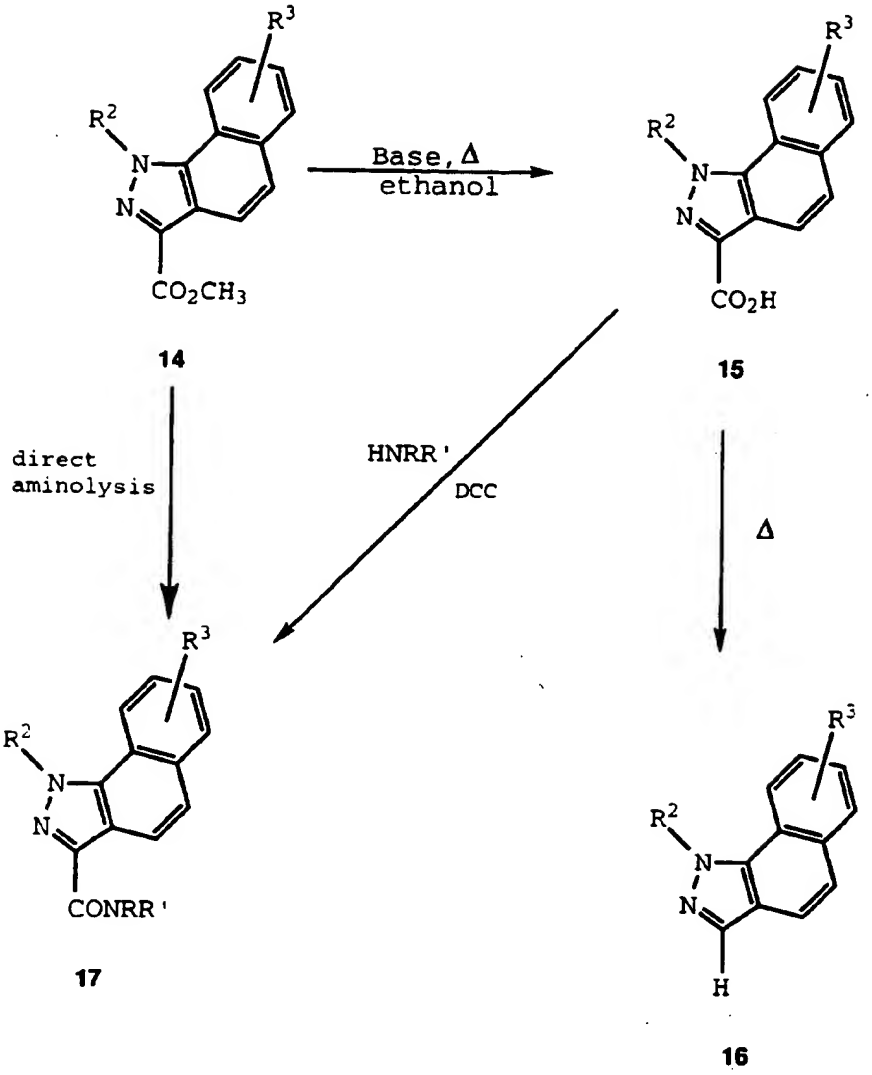
SCHEME IV



11 **12** **13**

Synthetic Scheme IV shows the two step procedure for preparation of substituted heteroarylhydrazine compounds **13** as used in Scheme I where R^2 is thienyl. In step 1, the heteroarylthionyl chloride **11** (where LG represents a leaving group such as halo) is treated with ammonia to give the heteroaryl sulfonamides **12**. In step 2, the heteroaryl sulfonamides **12** are treated with hydrazine to give the substituted heteroarylhydrazines **13**.

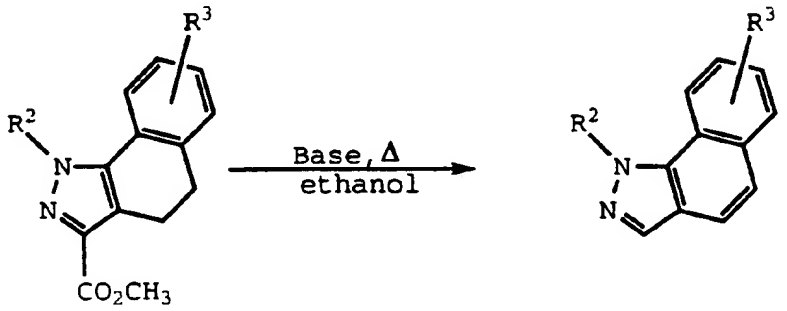
SCHEME V



Synthetic Scheme V shows procedures for preparing antiinflammatory agents **15**, **16** and **17** of Formula I. The esters **14**, which can be prepared as shown in Scheme I, are dissolved in aqueous ethanol and a base such as 10% NaOH is added. The reaction is heated to reflux to give the acids **15**. The acids **15** can be decarboxylated to the fused pyrazole **16** by heating to about 290°C. The acids **15** can be converted to the appropriate amides **17** by dissolving in methanol and treating with an appropriate amine in

the presence of a coupling agent such as dicyclohexylcarbodiimide (DCC). The amides **17** can also be prepared directly from esters **14** by treating with an appropriate amine.

SCHEME VI

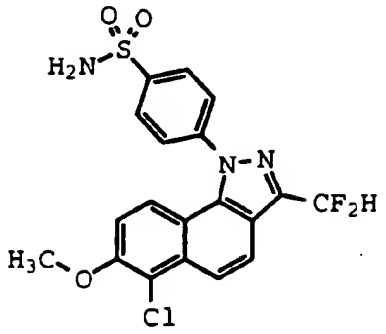


14 **18**

Synthetic Scheme VI shows procedures for preparing antiinflammatory agents **18** of Formula I. The dihydrobenzindazole esters **14**, which can be prepared similar to that shown in Scheme I and as shown in Hamilton, *J.Heterocyclic Chem.*, **13**, 545 (1976), are dissolved in ethanol and a base such as 10% NaOH is added. The reaction is heated to reflux to give the decarboxylated agents **18**.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I-II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

Example 1



4-[6-Chloro-3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide

Step 1 Preparation of 2-[2,2-difluoro-1-hydroxyethylidene]-3,4-dihydro-6-methoxy-1(2H)-naphthalenone

Ethyl difluoroacetate (6.2 g, 50 mmol) was dissolved in 75 mL of ether. To this solution was added 12 mL of 25% sodium methoxide in methanol (52.5 mmol). A solution of 6-methoxy-1-tetralone (8.81 g, 50 mmol) in 125 mL of ether was added over about 1 minute. The reaction mixture was stirred at room temperature for 14 hours and was diluted with 150 mL of 1N HCl. The phases were separated and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in 70 mL of boiling ethanol/water and cooled to room temperature, whereupon crystals of 2-[2,2-difluoro-1-hydroxyethylidene]-3,4-dihydro-6-methoxy-1(2H)-naphthalenone (also known as 6-methoxy-2-difluoroacetyl-1-tetralone) formed which were isolated by filtration and air dried (10.8 g, 85%): mp 52-54°C.

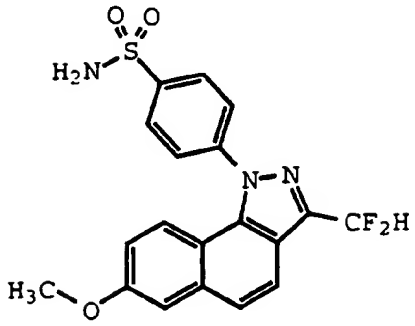
Step 2 Preparation of 4-[3-(difluoromethyl)-4,5-dihydro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide

3,4-Dihydro-6-methoxy-2-[2,2-difluoro-1-hydroxyethylidene]-1(2H)-naphthalenone from Step 1 (2.54 g, 10 mmol) was added to 4-sulfonamidophenylhydrazine hydrochloride (2.91 g, 13 mmol) and 250 mL of absolute ethanol. The solution was warmed to reflux for 15 hours and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and with brine, dried over anhydrous $MgSO_4$, filtered and reconcentrated *in vacuo*. The residue was recrystallized from a mixture of ethanol and water to give 4-[3-(difluoromethyl)-4,5-dihydro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide (3.3 g, 82%): mp 256-257°C.

Step 3 Preparation of 4-[6-chloro-3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide

4-[3-(Difluoromethyl)-4,5-dihydro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide (1.0 g, 1.23 mmol) from Step 2 was suspended in chloroform (100 ml), and N-chlorosuccinimide (NCS) (329 mg, 1.23 mmol) was added. The reaction was heated to 50°C for 16 hours. At this point, ethanol (20 ml) was added to dissolve the suspended reagents. The reaction was again heated to 50°C for 24 hours. An additional equivalent of NCS (329 mg) was added, and the reaction was heated to 50°C for an additional 4 days. Upon cooling, a precipitate which had formed was collected. This solid was pure 4-[6-chloro-3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide (350 mg, 65%): ^1H NMR (acetone d_6) δ = 4.0 (s, 3H), 7.2 (t, 1H, j = 54.0 Hz), 7.3 (d, 1H j = 9.3 Hz), 7.6 (d, 1H j = 9.3 Hz), 7.9 (d, 2H j = 8.7 Hz), 8.0 (d, 1H j = 9.3 Hz), 8.1 (d, 1H j = 9.3 Hz), 8.2 (d, 2H j = 8.7 Hz); ^{19}F NMR (acetone d_6) δ -113.5 ppm (d, 2F).

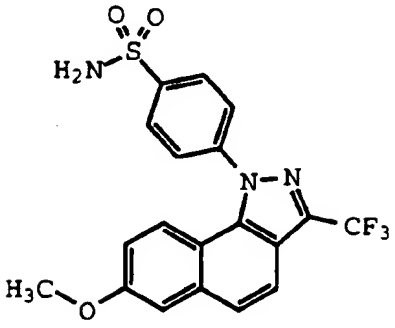
Example 2



4-[3-(Difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide

4-[3-(Difluoromethyl)-4,5-dihydro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide (Example 1, Step 2) (600 mg, 1.5 mmol) was dissolved in 1,4-dioxane (200 ml), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (341 mg, 1.5 mmol) was added. The reaction was heated to reflux for 16 hours, a second equivalent of DDQ (340 mg, 1.5 mmol) was added and the reaction was heated to reflux for an additional 24 hours. At three successive 24 hour intervals, 1.5 mmol additional DDQ was added and heating continued until no starting material was left (as determined by thin layer chromatography). The reaction was cooled to room temperature, at which time most of the hydroquinone by-product precipitated. The reaction was filtered and concentrated. The residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexane to yield 4-[3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide (514 mg, 85 %): ^{1}H NMR (acetone d_6) δ = 3.9 (s, 3H), 7.05 (m, 1H), 7.2 (t, 1H j = 54.0 Hz), 7.5 (m, 2H), 7.7 (m, 1H), 7.9 (m, 3H), 8.2 (d, 2H, j = 8.7 Hz); ^{19}F NMR (acetone d_6) δ -113.3 ppm (d, 2F).

Example 3



4-[7-Methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

Step 1 Preparation of 3,4-dihydro-6-methoxy-2-[2,2,2-trifluoro-1-hydroxyethylidene]-1(2H)-naphthalenone

6-Methoxytetralone (16.06 g, 91 mmol) was dissolved in ether (150 mL) and tetrahydrofuran (THF) (25 mL), and treated with ethyl trifluoroacetate (14.69 g, 103 mmol) and a sodium methoxide solution (25% in methanol, 24.44 g, 113 mmol). The reaction was stirred for 67.2 hours at room temperature, then treated with 3N HCl (40 mL). The organic layer was collected, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a brown solid which was recrystallized from ethanol/water to give the diketone as orange needles (19.67 g, 79%): mp 77-79°C; ^1H NMR ($CDCl_3$) 300 MHz 16.01 (br s, 1H) 7.93 (d, J=8.9 Hz, 1H) 6.87 (dd, J=8.7 Hz J=2.6 Hz, 1H) 6.73 (d, J=2.4 Hz, 1H) 3.87 (s, 3H) 2.86 (m, 2H) 2.74 (m, 2H); ^{19}F NMR ($CDCl_3$) 300 MHz -71.38 (s). Mass Spectrum M^+ = 273.0688

Step 2 Preparation of 4-[4,5-dihydro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

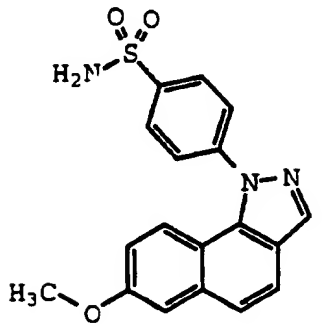
4-Sulfonamidophenylhydrazine hydrochloride (4.35 g, 19.4 mmol) was added to a stirred solution of 3,4-

dihydro-6-methoxy-2-[2,2,2-trifluoro-1-hydroxyethylidene]-1(2H)-naphthalenone from Step 1 (5.06 g, 18.6 mmol) in ethanol (100 mL). The reaction was heated to reflux and stirred for 16 hours. The reaction mixture was filtered and washed with ethanol to give the desired pyrazole as a white solid (6.97 g, 88%): mp 277-278°C; ^{1}H NMR (acetone d_6) 300 MHz 8.09 (d, J=8.7 Hz, 2H) 7.80 (d, J=8.9 Hz, 2H) 7.00 (d, J=2.6 Hz, 1H) 6.78 (m, 3H) 6.69 (dd, J=8.7 Hz J=2.6 Hz, 1H) 3.81 (s, 3H) 3.04 (m, 2H) 2.84 (m, 2H); ^{19}F NMR (acetone d_6) 300 MHz -62.43 (s). Mass Spectrum M^+ = 423.0838.

Step 3 Preparation of 4-[7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

4-[4,5-Dihydro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide from Step 2 (1.27 g, 3.0 mmol) was dissolved in 1,4-dioxane (200 ml), and DDQ (681 mg, 3.0 mmol) was added. The reaction was heated to reflux for 16 hours at which time a second equivalent of DDQ (681 mg, 3.0 mmol) was added and the reaction was heated to reflux for an additional 24 hours. At three successive 24 hour intervals, 3.0 mmol additional DDQ was added and heating continued until no starting material was left (as determined by thin layer chromatography). The reaction was cooled to room temperature at which time most of the hydroquinone by-product precipitated. The reaction was filtered and concentrated. The residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexane to yield 4-[7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide (1.1 g, 87%): ^{1}H NMR (acetone d_6) δ = 3.9 (s, 3H), 6.9 (broad s, 2H) 7.1 (m, 1H), 7.6 (m, 2H), 7.8 (m, 2H), 8.0 (d, 2H j = 8.7 Hz), 8.2 (d, 2H j = 8.7 Hz); ^{19}F NMR (acetone d_6) δ -61.8 ppm (s, 3F).

Example 4



4-[7-Methoxy-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide

Step 1. Preparation of 2-carbomethoxy-6-methoxy-1-tetralone.

A solution of 6-methoxy-1-tetralone (10.0 g, 0.057 mol) and dimethyl oxalate (7.37 g, 0.062 mol) in 100 mL of methanol was treated with a solution of 25% sodium methoxide in methanol. The solution was stirred at room temperature for 16 hours. The dark mixture was treated with 60 mL of 6 N hydrochloric acid, whereupon a precipitate formed that was isolated by filtration and air dried to provide 8.65 g (58%) of 2-carbomethoxy-6-methoxy-1-tetralone that was judged to be of sufficient purity to take onto the next step without further purification: ^{1}H NMR ($CDCl_3$/300 MHz) 7.99 (1H, d, J=8.66 Hz), 6.87 (1H, dd, J=8.66, 2.42 Hz), 6.72 (1H, d, J=2.42 Hz), 3.91 (3H, s), 3.88 (3H, s), 2.97 (2H, m), 2.86(2H, m).

Step 2. Preparation of 4,5-dihydro-meth: -[3-,carbomethoxy)-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide.

A solution of 2-carbomethoxy-6-methoxy-1-tetralone from Step 1 (6.00 g, 22.9 mmol) in 30 mL of anhydrous methanol was warmed to reflux and treated with 4-sulfonamidophenylhydrazine

hydrochloride (5.63 g, 25.2 mmol). The solution was maintained at reflux for 14 hours and cooled to room temperature, whereupon the desired pyrazole separated from solution, was isolated by filtration and air dried to afford 8.29 g (88%) of 4,5-dihydro-4-[3-(carbomethoxy)-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide: ^{1}H NMR ($CDCl_3$/300 MHz) 7.96 (2H, d, J=8.66 Hz), 7.59 (2H, d, J=8.66 Hz), 6.78 (1H, d, J=2.62 Hz), 6.71 (1H, d, J=8.66 Hz), 6.49 (1H, dd, J=8.66, 2.62 Hz), 6.43 (2H, s), 3.86 (3H, s), 3.70 (3H, s), 2.97 - 2.97 (4H, m). Mass spectrum M+H = 414. Anal. Calc'd. for $C_{20}H_{19}N_3O_5S$: C, 58.1; H, 4.63; N, 10.16; S, 7.75. Found: C, 58.20; H, 4.59; N, 10.19; S, 7.69.

Step 3. Preparation of 4,5-dihydro-7-methoxy-4-[3-(carboxy)-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide.

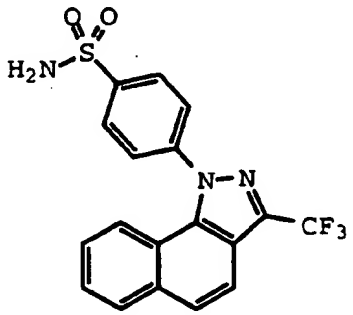
A solution of 4,5-dihydro-4-[3-(carbomethoxy)-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide from Step 2 (3.00 g, 7.26 mmol) in 25 mL of dioxane was treated with 2.5 N sodium hydroxide (7.3 mL, 18.1 mmol) and 5 mL of water. The solution was warmed to reflux and after 1 hour the solution was cooled to room temperature and acidified by the addition of excess 6 N hydrochloric acid. The acid separated as a white solid and was isolated by filtration and air dried to provide 2.41 g (83%) of pure acid that was used directly in the next step: ^{1}H NMR (CD_3OD): 8.09 (2H, d, J=8.66 Hz), 7.74 (2H, d, J=8.66 Hz), 6.96 (1H, d, J=2.62 Hz), 6.70 (1H, d, J=8.66 Hz), 6.60 (1H, dd, J=8.66, 2.62 Hz), 3.78 (3H, s), 3.01(4H, s). Mass spectrum M+H = 400.

Step 4. Preparation of 4-[7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide.

4,5-Dihydro-4-[3-(carboxy)-1*H*-benz[*g*]indazol-1-yl]benzenesulfonamide from Step 3 (1.00 g, 2.5 mmol)

was heated to 295°C for 0.5 hour. The residue was dissolved in a small amount of ethyl acetate and purified by flash chromatography, eluting with 40% ethyl acetate in hexane to give 4-[7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide as a white solid (200 mg, 20%): ^{1}H NMR (CD_3OD): 8.28 (1H, s), 8.18 (2H, d, J=8.66 Hz), 7.81 (1H, s), 7.77 (2H, d, J=8.66 Hz), 7.59 (1H, d, J=8.86 Hz), 7.52 (1H, d, J=9.27 Hz), 7.46 (1H, d, J=2.62 Hz), 7.0 (1H, dd, J=9.27, 2.62 Hz), 3.91 (3H, s). Mass spectrum M+H = 354. Anal. Calc'd. for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89; S, 9.07. Found: C, 60.93; H, 4.23; N, 11.73; S, 8.93.

Example 5



4-[3-(Trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

Step 1 Preparation of 3,4-dihydro-2-[2,2,2-trifluoro-1-hydroxyethylidene]-1(2H)-naphthalenone

To a solution of ethyl trifluoroacetate (28.4 g, 0.2 mol) and 75 mL of ether was added 48 mL of 25% sodium methoxide in methanol (0.21 mol). A solution of 1-tetralone (29.2 g, 0.2 mol) in ether (50 mL) was added over about 5 minutes The reaction mixture was stirred at room temperature for 14 hours and was diluted with 100 mL of 3N HCl. The phases were separated, and the organic layer was washed with 3N HCl and with brine,

dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in 70 mL of boiling ethanol/water and cooled to room temperature, whereupon crystals of 3,4-dihydro-2-[2,2,2-trifluoro-1-hydroxyethylidene]-1(2H)-naphthalenone formed which were isolated by filtration and air dried to give 32 g (81%) of pure 3,4-dihydro-2-[2,2,2-trifluoro-1-hydroxyethylidene]-1(2H)-naphthalenone: mp 48-49°C; ^1H NMR ($CDCl_3$) δ 2.8 (m, 2H), 2.9 (m, 2H), 7.2 (d, j = 3.0 Hz, 1H), 7.36 (m, 1H), 7.50 (m, 1H), 7.98 (m, 1H); ^{19}F NMR ($CDCl_3$) δ -72.0. EI GC-MS M^+ = 242.

Step 2 Preparation of 4,5-dihydro-4-[3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

3,4-Dihydro-2-[2,2,2-trifluoro-1-hydroxyethylidene]-1(2H)-naphthalenone from Step 1 (1.21 g, 5.0 mmol) was added to 4-sulfonamidophenylhydrazine hydrochloride (1.12 g, 5.0 mmol) and 25 mL of absolute ethanol. The solution was warmed to reflux for 15 hours, cooled and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and with brine, dried over anhydrous $MgSO_4$, filtered and reconcentrated *in vacuo*. The residue was recrystallized from a mixture of ethyl acetate and isooctane to give 1.4 g (71%) of pure 4,5-dihydro-4-[3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide: mp 257-258°C; ^1H NMR ($CDCl_3/CD_3OD$, 4:1) δ 2.7 (m, 2H), 2.9 (m, 2H), 6.6 (m, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.16 (m, 1H), 7.53 (m, 2H), 7.92 (m, 2H); ^{19}F NMR $CDCl_3$ δ -62.5. FAB-MS M^+H = 394.

Step 3 Preparation of 4-[3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide

4,5-Dihydro-4-[3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide from Step 2 (393 mg, 1.0 mmol) was dissolved in 1,4-dioxane (50 ml), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (227 mg,

1.0 mmol) was added. The reaction was heated to reflux for 16 hours at which time a second equivalent of DDQ (227 mg, 1.0 mmol) was added and the reaction was heated to reflux for an additional 24 hours. At three successive 24 hour intervals, 1.0 mmol additional DDQ was added and heating continued until no starting material was left. The reaction was cooled to room temperature at which time most of the hydroquinone by-product precipitated. The reaction was filtered and concentrated. The residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexane to yield 4-[3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide (352 mg, 90%): ^{1}H NMR (acetone d_6) δ = 6.89 (broad s, 2H), 7.5 (m, 1H), 7.7 (m, 2H), 7.89 (s, 2H), 8.0 (d, 2H, j = 8.7 Hz), 8.15 (d, 1H, j = 8.3 Hz), 8.3 (d, 2H, j = 8.7 Hz); ^{19}F NMR (acetone d_6) δ -61.7 ppm (s, 3F).

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a

group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in **Non-steroidal Anti-Inflammatory Drugs**, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

TABLE I.

RAT PAW EDEMA

% Inhibition[1]

Example	
1	29
2	24

1- @ 30 mg/kg body weight

Evaluation of COX-1 and COX-2 activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x10e8) along with 200 ng of linearized

baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10E7 - 10E8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 x 10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio] -1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity:

COX activity was assayed as PGE_2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II.

Example	Human COX-2 ID_{50} μM	Human COX-1 ID_{50} μM
1	1	>100
2	<.1	.8
3	<.1	>100
4	>100	>100
5	>100	>100

Biological paradigms for testing the cytokine-inhibiting activity of these compounds are found in WO95/13067, published 18 May 1995.

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal

penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from

tubes or other contain rs. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

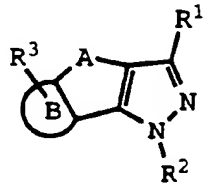
For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral

administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I



(I)

wherein A is $-(CH_2)_m-CH=CH-(CH_2)_n-$;

wherein m is 0 or 1;

wherein n is 0 or 1;

wherein B is selected from aryl and heteroaryl;

wherein R^1 is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, alkoxycarbonyl, carboxyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, aminocarbonyl, alkoxy, alkoxyalkyl, aminocarbonylalkyl, N-monoalkylaminocarbonyl, N-monoarylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, and heterocyclic;

wherein R^2 is selected from aryl and heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from alkylsulfonyl, aminosulfonyl, halo, alkyl, alkoxy, hydroxyl, and haloalkyl; and

wherein R^3 is one or more radicals selected from hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, aminocarbonyl, N-monoalkylaminocarbonyl, N-monoarylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, haloalkyl, hydroxyl,

alkoxy, hydroxyalkyl, haloalkoxy, aminosulfonyl, N-alkylaminosulfonyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro, and acylamino;

provided R^2 is substituted when R^3 is halo;

or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein A is $-(CH_2)_m-CH=CH-(CH_2)_n-$; wherein B is selected from aryl, five and six membered heteroaryl; wherein m is 0 or 1; wherein n is 0 or 1; wherein R^1 is selected from halo, lower haloalkyl, cyano, nitro, formyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, amidino, cyanoamidino, lower alkoxy, lower alkoxyalkyl, lower aminocarbonylalkyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylcarbonyl, lower alkylcarbonylalkyl, lower hydroxyalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkylthioalkyl, lower alkylsulfinylalkyl, lower alkylsulfonylalkyl, lower N-alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, lower N,N-dialkylaminosulfonyl, lower N-alkyl-N-phenylaminosulfonyl and five-seven membered heterocyclic; wherein R^2 is selected from phenyl and five or six membered heteroaryl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals selected from lower alkylsulfonyl, aminosulfonyl, hydrido, halo, lower alkyl, lower alkoxy, hydroxyl and lower haloalkyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower

alkoxy, lower hydroxyalkyl, lower haloalkoxy, aminosulfonyl, lower N-alkylaminosulfonyl, amino, lower N-alkylamino, lower N,N-dialkylamino, five-seven membered heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

3. Compound of Claim 2 wherein A is -CH=CH-; wherein B is selected from aryl and six membered heteroaryl; wherein R^1 is selected from halo, lower haloalkyl, cyano, nitro, formyl, lower alkoxycarbonyl, lower carboxyalkyl, lower alkoxy, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylcarbonyl and lower hydroxyalkyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected from lower alkylsulfonyl and aminosulfonyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, lower alkylsulfonyl, cyano, carboxyl, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N-alkylamino, lower N,N-dialkylamino, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

4. Compound of Claim 3 wherein A is -CH=CH-; wherein B is phenyl or pyridyl; wherein R^1 is selected from lower haloalkyl, cyano, lower alkoxycarbonyl, lower hydroxyalkyl, lower N-monoalkylaminocarbonyl, N-phenylaminocarbonyl, lower N,N-dialkylaminocarbonyl and lower N-alkyl-N-phenylaminocarbonyl; wherein R^2 is phenyl substituted at a substitutable position with a radical selected

from lower alkylsulfonyl and aminosulfonyl; and wherein R^3 is one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower alkoxycarbonyl, aminocarbonyl, lower N-monoalkylaminocarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, amino, lower N,N-dialkylamino and nitro; or a pharmaceutically-acceptable salt thereof.

5. Compoud of Claim 4 wherein A is -CH=CH-; wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, cyano, hydroxymethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl and N-methyl-N-phenylaminocarbonyl; wherein R^2 is phenyl substituted at a substitutable position with methylsulfonyl or aminosulfonyl; and wherein R^3 is one or more radicals selected from fluoro, chloro, bromo, methylthio, ethylthio, isopropylthio, *tert*-butylthio, isobutylthio, hexylthio, methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, *tert*-butylsulfinyl, isobutylsulfinyl, hexylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, hexyl, cyano, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, N-methylaminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl,

difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, trifluoromethoxy, amino, N,N-dimethylamino and nitro; or a pharmaceutically-acceptable salt thereof.

6. Compound of Claim 5 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

4-[6-chloro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

[1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carbonitrile;

methyl [1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

N-methyl [1-(4-aminosulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxamide;

6-chloro-7-methoxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

[1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carbonitrile;

ethyl [1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxylate;

N-methyl [1-(4-methylsulfonylphenyl)-6-chloro-7-methoxy-1H-benz[g]indazol-3-yl]carboxamide;

7-chloro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-7-fluoro-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-7-methyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-7-methoxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-6,7-methylenedioxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;

3-(difluoromethyl)-6-fluoro-7-methoxy-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6-chloro-3-(difluoromethyl)-7-fluoro-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6-chloro-3-(difluoromethyl)-7-methyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
3-(difluoromethyl)-6-fluoro-7-methyl-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6,7-dichloro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
6,7-difluoro-3-(difluoromethyl)-1-(4-methylsulfonylphenyl)-1H-benz[g]indazole;
[1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;
methyl [1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;
7-chloro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
7-fluoro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
7-methyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
7-methoxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
6,7-methylenedioxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
6-fluoro-7-methoxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
6-chloro-7-fluoro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
6-chloro-7-methyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
6-fluoro-7-methyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;
6,7-dichloro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6,7-difluoro-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-1-(4-methylsulfonylphenyl)-7-methylthio-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-7-methylsulfinyl-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

6-chloro-7-methoxy-1-(4-methylsulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazole;

[1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;

methyl [1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;

[1-(4-aminosulfonylphenyl)-3-(difluoromethyl)-1H-benz[g]indazol-7-yl]carbonitrile;

4-[7-chloro-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-fluoro-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-bromo-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-6,7-methylenedioxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-6-fluoro-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-fluoro-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-6-fluoro-7-methyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6,7-dichloro-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6,7-difluoro-3-(difluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-methylthio-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-3-(difluoromethyl)-7-methylsulfinyl-1H-benz[g]indazol-1-yl]benzenesulfonamide;

[1-(4-aminosulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylic acid;

methyl [1-(4-aminosulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carboxylate;

[1-(4-aminosulfonylphenyl)-3-(trifluoromethyl)-1H-benz[g]indazol-7-yl]carbonitrile;

4-[7-chloro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-fluoro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6,7-methylenedioxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[7-dimethylamino-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-fluoro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-7-fluoro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-chloro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6-fluoro-7-methyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

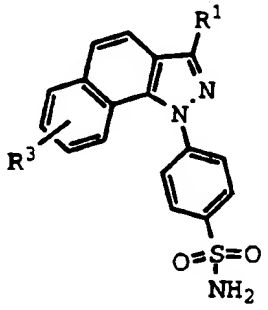
4-[6,7-dichloro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;

4-[6,7-difluoro-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-chloro-7-methylthio-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide;
4-[6-chloro-7-methylsulfinyl-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide; and
4-[6-chloro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide.

7. Compound of Claim 5 which is 4-[6-chloro-7-methoxy-3-(trifluoromethyl)-1H-benz[g]indazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

8. Compound of Claim 5 which is 4-[3-(difluoromethyl)-7-methoxy-1H-benz[g]indazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

9. A compound of Formula II



(II)

wherein R^1 is hydrido or haloalkyl; and wherein R^3 is one or more radicals selected from alkyl, alkoxy and halo; or a pharmaceutically-acceptable salt thereof.

10. Compound of Claim 9 wherein R^1 is hydrido or lower haloalkyl; and wherein R^3 is one or more radicals selected from lower alkyl, lower alkoxy and halo; or a pharmaceutically-acceptable salt thereof.

11. Compound of Claim 10 wherein R^1 is selected from hydrido, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; and wherein R^3 is one or more radicals selected from fluoro, chloro, bromo, methyl, ethyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy and *tert*-butoxy; or a pharmaceutically-acceptable salt thereof.

12. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9; or a pharmaceutically-acceptable salt thereof.

13. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 1; further provided that R^3 is not hydrido when R^1 is trifluoromethyl; and further provided that R^1 is not hydrido when R^3 is a single methoxy radical; or a pharmaceutically-acceptable salt thereof.

14. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Claim 2, 3, 4, 5, 6, 7, 8, or 9; or a pharmaceutically-acceptable salt thereof.

15. The method of Claim 13 for use in treatment of inflammation.

16. The method of Claim 13 for use in treatment of an inflammation-associated disorder.

17. The method of Claim 16 wherein the inflammation-associated disorder is arthritis.

18. The method of Claim 16 wherein the inflammation-associated disorder is pain.

19. The method of Claim 16 wherein the inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/US 95/11402

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/54 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 113, no. 5, 30 July 1990, Columbus, Ohio, US; abstract no. 40087s, E. BECALLI ET AL. 'Rearrangements of non-indoliziable arylhydrazones of methoxy-substituted aromatic carbonyl compounds in polyphosphoric acid.' page 560 ;column 2 ; see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 13512CS: RN's [128064-81-3] and [128064-78-8] & J. CHEM. RES., SYNOP., no.1, 1990 page 8 --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 1995	-4. 01. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/US 95/11402

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 65, no. 13, 19 December 1966, Columbus, Ohio, US; abstract no. 20134c, 'Pyrroloindazole derivatives.' see 20134f: compounds of formula I, wherein R, R2 are Ph, CH2Ph and Ph, H & NL,A,6 600 752 (AMERICAN CYANAMID CO.) 25 August 1966 ---	1,2
A	WO,A,94 15932 (G.D. SEARLE & CO.) 21 July 1994 see page 76 - page 78; claim 1 see page 8, line 6 - line 10 ---	1,9, 12-19
A	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol.13, no.3, June 1976, PROVO US pages 545 - 553 R.W. HAMILTON 'The Antiarrhythmic and Antiinflammatory Activity of a Series of Tricyclic Pyrazoles' cited in the application see the whole document; in particular page 548, table III, compound no. 48; page 548 table IV, compound no. 60; and page 549, table V, compound no. 75 -----	1,9, 12-19

1

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US95/11402

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Altough claims 13-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Intern... il Application No
PCT/US 95/11402

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
NL-A-6600752	25-08-66	BE-A-	676991	24-08-66
		CH-A-	477464	31-08-69
		DE-A-	1645892	17-09-70
		FR-M-	5500	30-10-67
		FR-A-	1476735	23-06-67
		GB-A-	1065183	
		US-A-	3404157	01-10-68
WO-A-9415932	21-07-94	AU-B-	6027694	15-08-94
		CA-A-	2152792	21-07-94
		EP-A-	0679157	02-11-95